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EDITORIAL COMMENT

Predicting Mortality in Pulmonary Arterial Hypertension

Can It Really Be That Simple?*

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Echocardiography plays an important role in the diagnosis and monitoring of cardiac structure and function in patients with pulmonary arterial hypertension (PAH) (1). The routine application of resting echocardiography allows for the noninvasive assessment of pulmonary and right ventricular (RV) pressures, as well as the determination of the progression of (mal)adaptive remodeling of the RV cavity (2). Although there is a clear link between the severity of the disease and the extent of RV remodeling, there is limited evidence to suggest that echocardiography alone has prognostic value. Some large studies have attempted to develop a predictive model for mortality risk stratification in PAH and established that echocardiography is mainly redundant. In 1991, the National Institutes of Health provided the first prognostic equation; however, in view of changes in disease classifications and an advancement in both therapy and technology, the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) study in 2010 (3) provided a more up-to-date mortality risk stratification model for PAH. This model utilizes a range of demographic, clinical, and diagnostic criteria, providing reasonable sensitivity and specificity. That aside, the criteria are numerous and the model is complex, requiring the use of multiple investigations with little reliance on the structural or functional remodeling of the RV. Furthermore, a relatively recent statement from the American College of Cardiology Foundation stated that echocardiography alone holds little predictive value (4). From a pathophysiological viewpoint, these findings appear somewhat surprising. PAH leads to what we consider a right heart failure syndrome, and therefore we would expect the degree of RV remodeling and dysfunction to be directly linked to mortality, as is the case in left-sided heart failure. In addition, exercise limitation is a strong predictor of prognosis in PAH (2), whereas right ventricular failure contributes significantly to reduced exercise tolerance primarily through a reduced cardiac index but also secondary to peripheral fluid retention.

The disparity between what we expect and what we observe should lead one to question the validity of the applied measurements. In this setting, the applied measurements relate to the assessment of right heart structure and function. It is feasible that previous work has failed to acknowledge the complex holistic nature of the right heart and the interaction between the right atrium (RA) and the RV. Moreover, the complex shape of the RV and its fiber alignment dictates equally complex mechanics. RV function is influenced by a range of factors, including those that affect preload and afterload, such as respiration, gravity, pulmonary vascular resistance, and direct factors related to the structural integrity of the right-sided myocardium, such as intrinsic contractility, relaxation, and compliance (5). In the presence of an acute increase in RV afterload, the workload of the ventricle increases, causing prolonged isovolumic time periods that are normally minimal. In turn, this directly influences the RA-RV relationship, causing a reduction in the RA-RV pressure gradient and reducing the overall early diastolic flow and ultimately reducing the kinetic energy available for ejection. This makes the RV less energy efficient. Consequently, a change will occur in RA volumes across the cardiac cycle to increase preload or alternatively enhance the active booster function. When faced with a chronic elevation in RV afterload, as seen in PAH, the RV remodels and changes its

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mechanical contribution to output; however, this further influences the RA-RV relationship, with dilation of the RA a likely manifestation. It is this consideration of the complexity of load, the RA-RV interaction, and RV structural and functional remodeling that is frequently lacking.

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In this issue of *iJACC*, Haddad et al. (6) provided a comprehensive assessment of right heart structure and function using 2-dimensional (2D) and Doppler echocardiography in 95 patients with idiopathic, familial, or drug- and toxin-associated PAH. This exploratory study was aimed at determining which parameters act as independent predictors of outcome and secondly deriving an echocardiographic score that would best predict mortality in these patients. RV structure was assessed using linear dimensions and area, whereas function was determined by right ventricular fractional area change (RVFAC), tricuspid plane systolic excursion, and myocardial performance index. In addition, RA area was assessed throughout the cardiac cycle, providing total, passive, and emptying fractions, as well as a value of maximum size. Composite endpoints of death or lung transplantation were assessed at 1, 3, and 5 years. A range of parameters were associated with the composite endpoint, and subsequently RV function as assessed through RVFAC, RA area index, and systolic blood pressure collectively provided a strong model for prediction of mortality and were considered the optimal variables to generate a "right heart" score. Importantly, there was also a strong association between RA active emptying fraction and the composite endpoint. Furthermore, when the right heart score was validated against the National Institutes of Health registry score and the REVEAL score, it provided similar accuracy but superior sensitivity and specificity.

It is important to note that this "simple" index is simple from a practical perspective in that a single investigation is all that was required; however, the findings reflect the complexity of the right heart. RVFAC was more readily associated with outcomes than tricuspid plane systolic excursion, highlighting the fact that this measurement takes into account both radial and longitudinal functions. It is therefore sensible to assume that indexes that better reflect overall RV function will improve the prognostic value of the right heart score. Recent advances in quantitative analysis such as strain imaging have been shown to relate strongly to RV function in patients with PAH (7). Although current 2D technology only provides accurate RV longitudinal information, a recent study using multiple views to provide a more comprehensive assessment of RV mechanics was proposed and successfully identified RV dysfunction in patients with PAH (8). Other techniques such as deformation-volume relationships are time consuming but again may provide additional value. 3D imaging of the RV is now feasible, and hence, RV ejection fraction and 3D strain are becoming part of the noninvasive armamentarium. Although RV size did not show any strong association with outcome, it is clear that a 3D technique would allow for a more detailed understanding of complex RV remodeling (9). It is also apparent that these tools have recently been applied to the RA (10,11), and therefore, a greater depth of knowledge pertaining to the RA-RV relationship is rapidly becoming reality.

The next logical step should aim to use the advances in echocardiography without detracting from the "simple" nature of the index. It is important to commend Haddad et al. (6) for this work and for reminding us that "simple" can still reflect complexity but also to be aware that any index needs to be sensitive to responses to therapy and disease progression while remaining valid and reproducible.

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REFERENCES

1. Badano LP, Ginghina C, Easaw J, et al. Right ventricle in pulmonary arterial hypertension: haemodynamics, structural changes, imaging, and proposal of a study protocol aimed to assess remodelling and treatment effects. Eur J Echocardiogr 2010;11:27–37.

2. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol 2013;62 Suppl:D22–33.

3. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72.

4. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62 Suppl: D42–50.

5. Sengupta PP, Narula J. RV form and function: a piston pump, vortex impeller, or hydraulic ram? J Am Coll Cardiol Img 2013;6:636–9.

6. Haddad F, Spruijt OA, Denault AY, et al. Right heart score for predicting outcome in idiopathic, familial, or drug- and toxin-associated pulmonary arterial hypertension. J Am Coll Cardiol Img 2015;8:627–38.

7. Borges AC, Knebel F, Eddicks S, et al. Right ventricular function assessed by two-dimensional

strain and tissue Doppler echocardiography in patients with pulmonary arterial hypertension and effect of vasodilator therapy. Am J Cardiol 2006; 98:530–4.

8. Rajagopal S, Forsha DE, Risum N, et al. Comprehensive assessment of right ventricular function in patients with pulmonary hypertension with global longitudinal peak systolic strain derived from multiple right ventricular views. J Am Soc Echocardiogr 2014;27:657–65.

9. Smith BCF, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P. Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 2014;64:41–51.

10. McClean G, George K, Lord R, et al. Chronic adaptation of atrial structure and function in elite male athletes. Eur Heart J Cardiovasc Imaging 2014;16:417–22.

11. Patel AR, Alsheikh-Ali AA, Mukherjee J, et al. 3D echocardiography to evaluate right atrial pressure in acutely decompensated heart failure correlation with invasive hemodynamics. J Am Coll Cardiol Img 2011;4:938–45.

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